

Application No.: 10/076,071

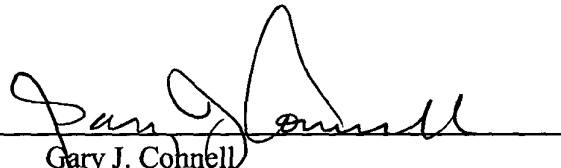
REMARKS

Claims are canceled in this Preliminary Amendment for the sole purpose of reducing the filing fees for the application. The claims are canceled without prejudice to or disclaimer of the subject matter thereof, and Applicants expressly reserve the right to pursue such claims in a continuing application.

Attached hereto is a marked up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version With Markings to Show Changes Made." Also, for the convenience of the Examiner and because the number of claims canceled in this Preliminary Amendment is quite large, Applicants have attached a clean version of the entire set of pending claims as set forth in 37 CFR § 1.211(c)(3).

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 2-52, 84-118, 120-123, 125-128, 130-133, 135-157, 159-181, 183-205, 207-233, 263-265, 267-269, 271-292, 294-315, 317-342, 344-369, 371-391, 393-414, and 416 have been cancelled.

82. (Amended) The method of [any one of Claims 53-81] Claim 53 wherein the cell, tissue or organ is transplanted into an animal after being contacted with the solution or medium containing the peptide.

Pending Claims
(Following Entry of Preliminary Amendment)

1. A method of reducing the damage done by reactive oxygen species (ROS) in an animal comprising administering to the animal an effective amount of a peptide having the formula:

$$P_1 - P_2,$$

wherein:

P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

n is 0-100;

or a physiologically-acceptable salt thereof.

53. A method of reducing the damage done by reactive oxygen species (ROS) to a cell, a tissue or an organ that has been removed from an animal comprising contacting the cell, tissue or organ with a solution or medium containing an effective amount of a peptide having the formula:

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$P_1 - P_2$,

wherein:

P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

n is 0-100;

or a physiologically-acceptable salt thereof.

54. The method of Claim 53 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine.

55. The method of Claim 53 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

56. The method of Claim 53 wherein Xaa₃ is lysine.

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57. The method of Claim 53 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

58. The method of Claim 57 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, leucine, or α -hydroxymethylserine.

59. The method of Claim 58 wherein Xaa₂ is alanine, threonine, leucine, or α -hydroxymethylserine.

60. The method of Claim 59 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

61. The method of Claim 53 wherein n is 0-10.

62. The method of Claim 61 wherein n is 0-5.

63. The method of Claim 62 wherein n is 0.

64. The method of Claim 53 wherein P₂ comprises a metal-binding sequence.

65. The method of Claim 64 wherein P₂ comprises one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,

(Xaa₄)_m His Xaa₂ Xaa₅,

(Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or

(Xaa₄)_m Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

66. The method of Claim 65 wherein Xaa₅ is Orn or Lys.

67. The method of Claim 64 wherein P₂ comprises one of the following sequences:

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

[(Xaa₄)_mXaa₅Xaa₂His]_r,

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃(Xaa₄)_mXaa₅Xaa₂His]_r, or

[(Xaa₄)_mXaa₅Xaa₂His(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂, m is 0-5 and r is 2-100.

68. The method of Claim 64 wherein P₂ comprises a sequence which binds Cu(I).

69. The method of Claim 68 wherein P₂ comprises one of the following sequences:

Met Xaa₄ Met,

Met Xaa₄ Xaa₄ Met,

Cys Cys,

Cys Xaa₄ Cys,

Cys Xaa₄ Xaa₄ Cys,

Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,

Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],

Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],

Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or

γ-Glu Cys Gly.

70. The method of Claim 69 wherein P₂ is Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9].

71. The method of Claim 53 wherein P₂ comprises a sequence which enhances the ability of the peptide to penetrate cell membranes, reach target tissues, or both.

72. The method of Claim 71 wherein P_2 is hydrophobic or an arginine oligomer.

73. The method of Claim 53 wherein at least one of the amino acids of P_1 other than β -alanine, when present, is a D-amino acid.

74. The method of Claim 73 wherein Xaa_1 is a D-amino acid, His is a D-amino acid, or both Xaa_1 and His are D-amino acids.

75. The method of Claim 74 wherein all of the amino acids of P_1 other than β -alanine, when present, are D-amino acids.

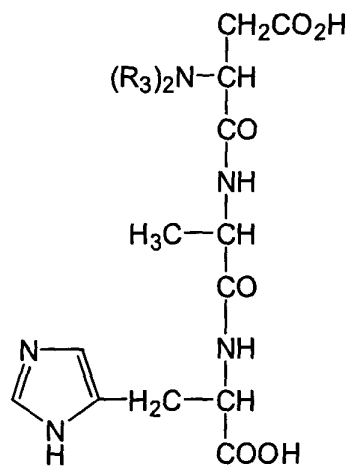
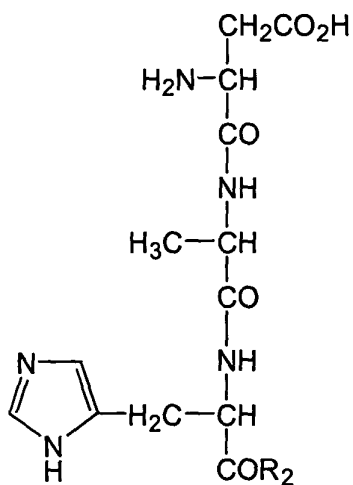
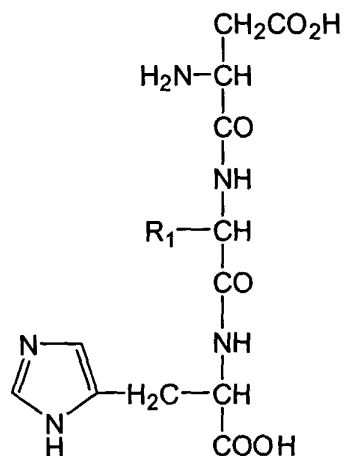
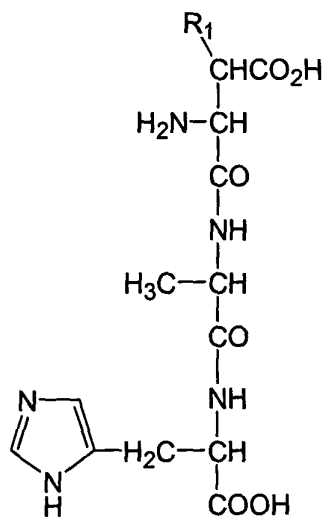
76. The method of Claim 73 wherein at least 50% of the amino acids of P_2 are D-amino acids.

77. The method of Claim 74 wherein at least 50% of the amino acids of P_2 are D-amino acids.

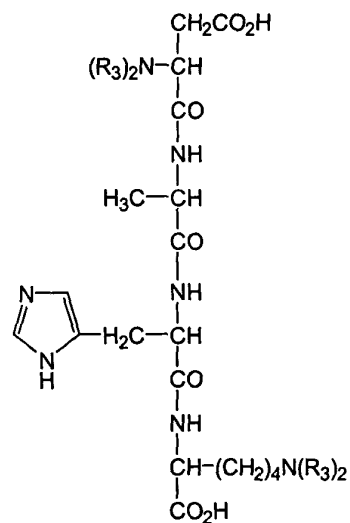
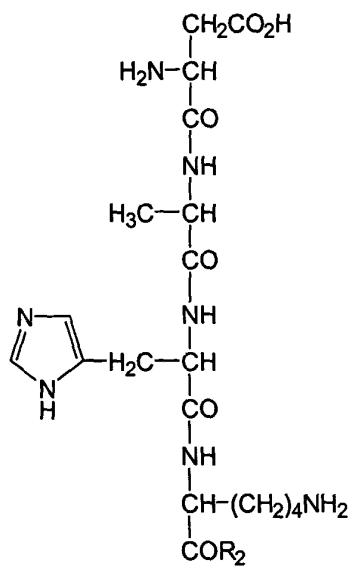
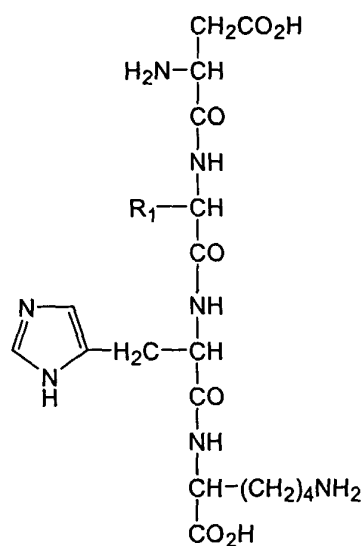
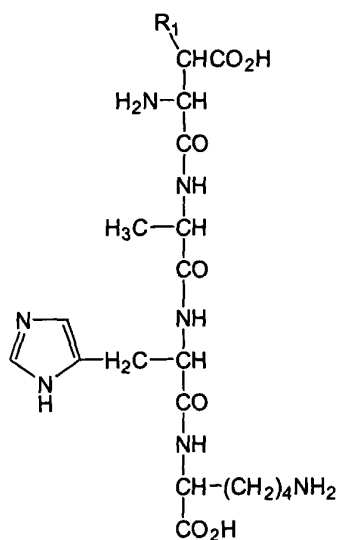
78. The method of Claim 75 wherein at least 50% of the amino acids of P_2 are D-amino acids.

79. The method of Claim 53 wherein at least one amino acid of P_1 , at least one amino acid of P_2 , or at least one amino acid of P_1 and at least one amino acid of P_2 , is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

80. The method of Claim 79 wherein n is 0 and P₁ has one of the following formulas:



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wherein:

R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-NH_2$, $-NHR_1$, $N(R_1)_2$, $-OR_1$, or R_1 ; and

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R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

81. The method of Claim 53 wherein the solution of medium further comprises an effective amount of another metal-binding compound in combination with the peptide.

82. The method of Claim 53 wherein the cell, tissue or organ is transplanted into an animal after being contacted with the solution or medium containing the peptide.

83. A method of reducing the concentration of a metal in an animal in need thereof comprising administering to the animal an effective amount of a peptide having the formula:



wherein:

P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

n is 0-100;

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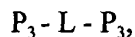
or a physiologically-acceptable salt thereof.

119. A method of reducing the damage done by reactive oxygen species (ROS) in an animal comprising administering to the animal an effective amount of a metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

124. A method of reducing the damage done by reactive oxygen species (ROS) to a cell, a tissue or an organ that has been removed from an animal comprising contacting the cell, tissue or organ with a solution or medium containing an effective amount of a metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

129. A method of reducing the concentration of metal in an animal in need thereof comprising administering to the animal an effective amount of a metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

134. A method of reducing the damage done by reactive oxygen species (ROS) in an animal comprising administering to the animal an effective amount of a metal-binding peptide dimer of the formula:



wherein:

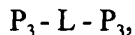
each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

158. A method of reducing the damage done by reactive oxygen species (ROS) to a cell, a tissue or an organ that has been removed from an animal comprising contacting the

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cell, tissue or organ with a solution or medium containing an effective amount of a metal-binding peptide dimer of the formula:

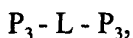


wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

182. A method of reducing the concentration of a metal in an animal in need thereof comprising administering to the animal an effective amount of a metal-binding peptide dimer of the formula:



wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

206. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a peptide having the formula:



wherein:

P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

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Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

n is 0-100;

or a physiologically-acceptable salt thereof.

234. A kit comprising a container holding a peptide having the formula:



wherein:

P₁ is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P₂ is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

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Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

n is 0-100;

or a physiologically-acceptable salt thereof.

235. The kit of Claim 234 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine.

236. The kit of Claim 234 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

237. The kit of Claim 234 wherein Xaa₃ is lysine.

238. The kit of Claim 234 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

239. The kit of Claim 238 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, leucine, or α -hydroxymethylserine.

240. The kit of Claim 239 wherein Xaa₂ is alanine, threonine, leucine, or α -hydroxymethylserine.

241. The kit of Claim 240 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

242. The kit of Claim 234 wherein n is 0-10.

243. The kit of Claim 242 wherein n is 0-5.

244. The kit of Claim 243 wherein n is 0.

245. The kit of Claim 234 wherein P_2 comprises a metal-binding sequence.

246. The kit of Claim 245 wherein P_2 comprises one of the following sequences:

$(Xaa_4)_m Xaa_3 His Xaa_2 Xaa_5$,

$(Xaa_4)_m His Xaa_2 Xaa_5$,

$(Xaa_4)_m Xaa_5 Xaa_2 His Xaa_3$, or

$(Xaa_4)_m Xaa_5 Xaa_2 His$,

wherein Xaa_5 is an amino acid having a free side-chain $-NH_2$ and m is 0-5.

247. The kit of Claim 246 wherein Xaa_5 is Orn or Lys.

248. The kit of Claim 245 wherein P_2 comprises one of the following sequences:

$[(Xaa_4)_m Xaa_5 Xaa_2 His Xaa_3]_r$,

$[(Xaa_4)_m Xaa_5 Xaa_2 His]_r$,

$[(Xaa_4)_m Xaa_5 Xaa_2 His Xaa_3 (Xaa_4)_m Xaa_5 Xaa_2 His]_r$, or

$[(Xaa_4)_m Xaa_5 Xaa_2 His (Xaa_4)_m Xaa_5 Xaa_2 His Xaa_3]_r$,

wherein Xaa_5 is an amino acid having a free side-chain $-NH_2$, m is 0-5 and r is 2-100.

249. The kit of Claim 245 wherein P_2 comprises a sequence which binds Cu(I).

250. The kit of Claim 249 wherein P_2 comprises one of the following sequences:

Met Xaa_4 Met,

Met $Xaa_4 Xaa_4$ Met,

Cys Cys,

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Cys Xaa₄ Cys,
Cys Xaa₄ Xaa₄ Cys,
Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,
Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],
Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],
Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or
 γ -Glu Cys Gly.

251. The kit of Claim 250 wherein P₂ is Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9].

252. The kit of Claim 234 wherein P₂ comprises a sequence which enhances the ability of the peptide to penetrate cell membranes, reach target tissues, or both.

253. The kit of Claim 252 wherein P₂ is hydrophobic or an arginine oligomer.

254. The kit of Claim 234 wherein at least one of the amino acids of P₁ other than β -alanine, when present, is a D-amino acid.

255. The kit of Claim 254 wherein Xaa₁ is a D-amino acid, His is a D-amino acid, or both Xaa₁ and His are D-amino acids.

256. The kit of Claim 255 wherein all of the amino acids of P₁ other than β -alanine, when present, are D-amino acids.

257. The kit of Claim 254 wherein at least 50% of the amino acids of P₂ are D-amino acids.

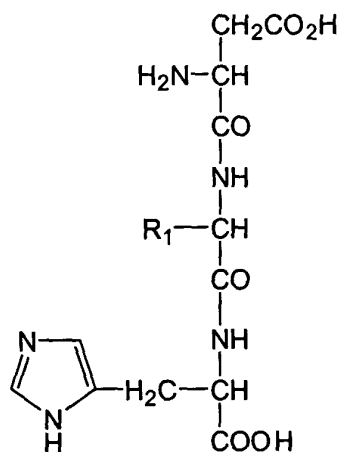
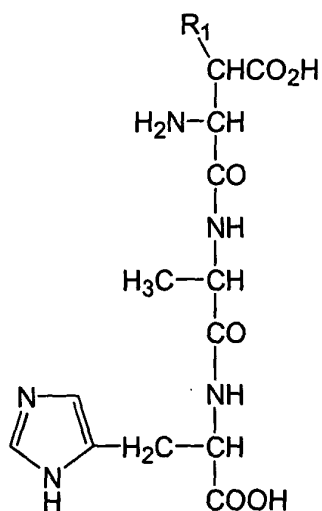
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258. The kit of Claim 255 wherein at least 50% of the amino acids of P_2 are D-amino acids.

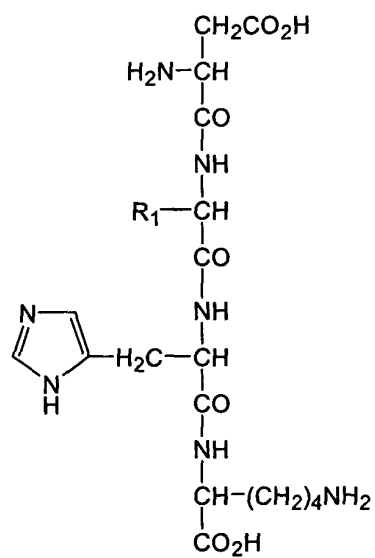
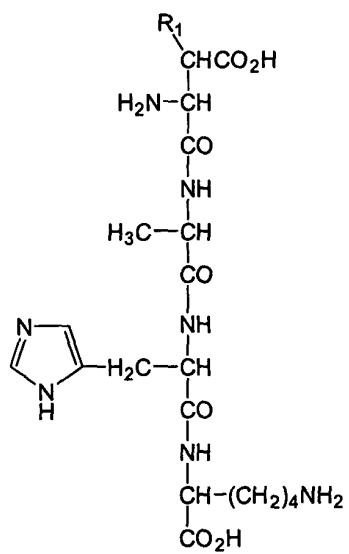
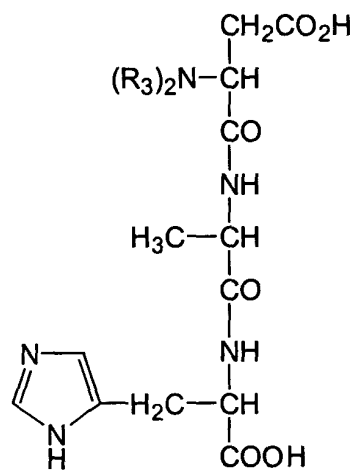
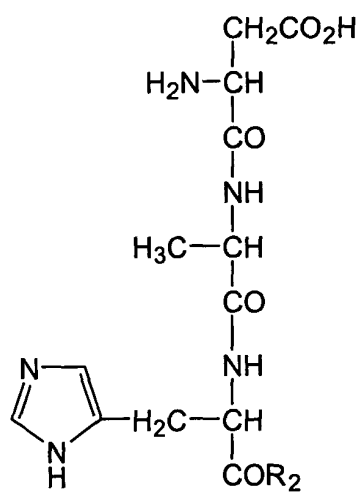
259. The kit of Claim 256 wherein at least 50% of the amino acids of P_2 are D-amino acids.

260. The kit of Claim 234 wherein at least one amino acid of P_1 , at least one amino acid of P_2 , or at least one amino acid of P_1 and at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that increases the ability of the peptide to bind metal ions.

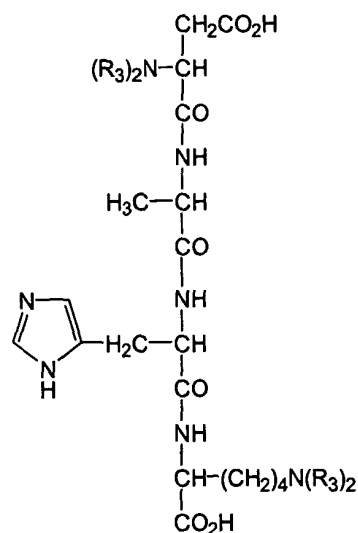
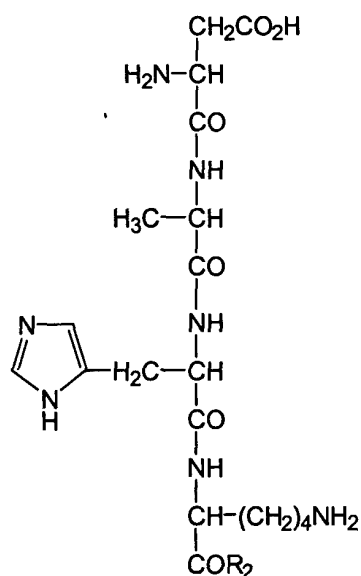
261. The kit of Claim 260 wherein n is 0 and P_1 has one of the following formulas:



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wherein:

R_1 is an alkyl, aryl, or heteroaryl;

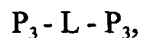
R_2 is $-\text{NH}_2$, $-\text{NHR}_1$, $\text{N}(\text{R}_1)_2$, $-\text{OR}_1$, or R_1 ; and

R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

262. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

266. A kit comprising a container holding a metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

270. A composition comprising a metal-binding peptide dimer of the formula:



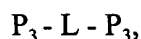
wherein:

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each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

293. A kit comprising a container holding a metal-binding peptide dimer of the formula:



wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

316. A peptide having the formula:



wherein:

P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

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Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

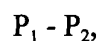
Xaa₄ is any amino acid;

n is 0-100; and

at least one amino acid of P₁ is a D-amino acid;

or a physiologically-acceptable salt thereof.

343. A peptide having the formula:



wherein:

P₁ is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P₂ is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α-hydroxymethylserine;

Xaa₂ is glycine, alanine, β-alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α-hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid;

n is 0-100; and

at least one amino acid of P₁, at least one amino acid of P₂, or at least one amino acid of P₁ and at least one amino acid of P₂ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₁ to bind metal ions, (b) a

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substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.;
or a physiologically-acceptable salt thereof.

370. A metal-binding peptide having the formula:



wherein:

P_1 is:

Xaa_1 Xaa_2 His: or

Xaa_1 Xaa_2 His Xaa_3 ;

P_2 is a peptide sequence which comprises the sequence of a metal binding site;

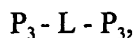
Xaa_1 is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa_2 is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine; and

Xaa_3 is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

or a physiologically-acceptable salt thereof.

392. A metal-binding peptide dimer of the formula:



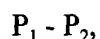
wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

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L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

415. A method of *in vitro* fertilization wherein a medium is utilized which comprises an amount of a peptide effective to reduce the damage done by reactive oxygen species, the peptide having the formula:



wherein:

P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

n is 0-100;

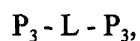
or a physiologically-acceptable salt thereof.

417. A method of *in vitro* fertilization wherein a medium is utilized which comprises an amount of a metal-binding peptide effective to reduce the damage done by reactive

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oxygen species, the metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

418. A method of *in vitro* fertilization wherein a medium is utilized which comprises an amount of a metal-binding peptide dimer effective to reduce the damage done by reactive oxygen species, the peptide dimer having the formula:



wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.